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Elastography: New Developments in Ultrasound for Predicting Malignancy in Thyroid Nodules

T. Rago, F. Santini, M. Scutari, A. Pinchera, and P. Vitti

Department of Endocrinology, University of Pisa, 56124 Pisa, Italy

Background: Elastography is a newly developed dynamic technique that uses ultrasound (US) to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. US elastography has been applied to differentiate malignant from benign lesions.

Patients: This study included 92 consecutive patients with a single thyroid nodule who underwent surgery for compressive symptoms or suspicion of malignancy on fine needle aspiration cytology. Tissue stiffness on US elastography was scored from one (greatest elastic strain) to five (no strain).

Results: On US elastography: scores 1 and 2 were found in 49 cases, all benign lesions; score 3 in 13 cases, one carcinoma and 12 benign lesions; and scores 4 and 5 in 30 cases, all carcinomas. Thus, the elasticity scores 4–5 were highly predictive of malignancy ($P < 0.0001$), with a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 98%. In 32 patients with an indeterminate fine needle aspiration result, the conventional US was not predictive of malignancy, while an US elastographic score of 4–5 was observed in six of seven (86%) patients with carcinoma on histology, and a score of 1–3 in all 25 patients with benign lesions.

Conclusions: US elastography has great potential as an adjunctive tool for the diagnosis of thyroid cancer, especially in indeterminate nodules on cytology. Larger prospective studies are needed to confirm these results and establish the diagnostic accuracy of this new technique **(*J Clin Endocrinol Metab* 92: 2917–2922, 2007)**

THYROID NODULES ARE common in people living in iodine sufficient areas, their prevalence being dramatically increased in iodine-deficient areas. The great majority of nodules are benign, less than 5% of them being malignant (1–9). Cytological examination of material obtained by fine needle aspiration (FNA), due to its high sensitivity and specificity, is the best single test for differentiating malignant from benign thyroid lesions (10–13). Yet, a substantial proportion of nodules are not correctly diagnosed before surgical treatment, and histological examination is required. Several studies have been performed to establish the ability of thyroid ultrasonography (US) to differentiate benign from malignant lesions (14–17). Indeed, as compared with FNA, thyroid US has the advantage of being a noninvasive procedure and giving immediate information. Among several US patterns, hypoechogenicity of the nodule, spot microcalcifications, and the absence of halo sign have been useful for predicting thyroid malignancy (14, 15). In a previous study, we reported that conventional US and color-flow Doppler become highly predictive of malignancy only when multiple patterns are simultaneously present in a thyroid nodule. However, the predictive value of US increases only at the expense of its sensitivity, and malignancy is predicted with high specificity by thyroid US only in less then 20% of patients (14). In the assessment of thyroid nodules, clinical evaluation is also very important. In particular, as reported by recent consensus, a firm or hard consistency is associated with an increased risk of malignancy (18–20). However, this clinical parameter is highly subjective and dependent on the experience of the examiner.

Elastography is a newly developed dynamic technique that uses US to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. US elastography has been applied to study the hardness/elasticity of nodules to differentiate malignant from benign lesions (21–24). A previous report on thyroid nodules concluded that off-line processed US elastograms may predict malignancy with 96% specificity and 82% sensitivity (25).

In this study we have evaluated 92 patients with thyroid nodules by real-time US elastography. The predictive value of this technique was calculated based on the histological results obtained after thyroidectomy.

Patients and Methods

Patients

The study included 92 consecutive patients (63 females, mean age 43 ± 15 yr, range 8–70, and 29 males, mean age 39 ± 12 yr, range 16–67) with a single thyroid nodule, seen from January 2006–2007 in the Department of Endocrinology, University of Pisa, who underwent surgery for compressive symptoms or suspicion of malignancy on FNA cytology. All patients gave their informed consent to participate in the study.

Serum calcitonin was undetectable in 91 patients and 243 pg/ml in one patient. All patients were euthyroid. FNA was performed under US guidance by a skilled endocrinologist using a 23-gauge needle attached to a 10-ml syringe. The material was air dried, stained with Papanicolaou and Giemsa, and interpreted by an experienced cytologist. The adequacy of aspirates was defined according to the guidelines of the Papanicolaou Society (26). The indications for surgery were: the size of nodules in 25 patients with cytology of benign lesion; an indeterminate (n = 32) or nondiagnostic cytology (n = 13); a cytological diagnosis suggestive (n = 15) or suspicious (n = 6) of papillary carcinoma; and suspected med-

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Abbreviations: FNA, Fine needle aspiration; US, ultrasound.

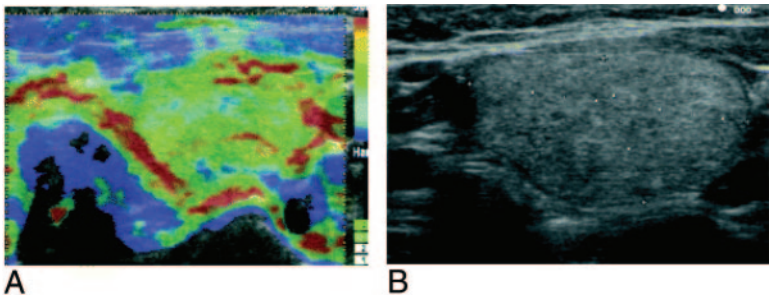

FIG. 1. Thyroid nodule images obtained on US elastography with elasticity score 1 (A) and conventional US (B).

ullary carcinoma in one case. US elastography was also performed in eight patients who were not included in the study group: four patients had nodules with coarse calcifications that almost substituted the nodule wall, and four had cystic nodules.

Thyroid conventional US and US elastography

Thyroid US and US elastography were performed using a real-time instrument (Hitachi EUB 8500 Logos system machine with a linear transducer with central frequency of ~10 MHz; Hitachi Medical Systems, Tokyo, Japan). A careful evaluation of the following US parameters was performed on all thyroid nodules: echogenicity (hyperechoic, isoechoic, or hypoechoic with respect to normal thyroid parenchyma, presence or absence of the halo sign); spot microcalcifications (presence of hyperechoic spots less than 2 mm, without acoustic shadowing); and color-flow Doppler pattern that was defined as absence of blood flow (type I), perinodular and absent or slight intranodular blood flow (type II), and marked intranodular and absent or slight perinodular blood flow (type III) (14).

US elastographic measurement was performed during the US examination, using the same real-time instrument and the same probe. The probe was placed on the neck with light pressure, and a box was highlighted by the operator that included the nodule to be evaluated. The principle of US elastography is to acquire two ultrasonic images (before and after tissue compression by the probe) and track tissue displacement by assessing the propagation of the imaging beam. A dedicated software (Combined Autocorrelation Method, Hitachi Medical Systems) able to provide an accurate measurement of tissue distortion was used. The US elastogram was displayed over the B-mode image in a color scale that ranges from red, for components with greatest elastic strain (*i.e.* softest components), to blue for those with no strain (*i.e.* hardest components) (Figs. 1 and 2). The US elastographic image was matched with an elasticity color scale and classified using the Ueno and Ito (27) elasticity score (Table 1). To minimize the interobserver and intraobserver variability, the freehand compression applied on the neck region was standardized by real-time measurement displayed on a numerical scale (graded 1 to 5; Figs. 1 and 2), to maintain an intermediate level optimal for US elastographic evaluation (3 to 4). It is important that the level of pressure is maintained constant throughout the examination. This technique is easy to perform and requires no more than 3–5 min of additional examination time. All examinations were performed by the same operator (T.R.), who was not aware of the results of cytology. Static and moving images were also recorded to be reviewed subsequently by a second skilled US examiner (P.V.). The agreement on the scoring of US parameter was more than 90% between the two observers. In particular, scoring by the two examiners was coincident in 83 of 92 patients. In nine cases the final score was agreed after conjoint reexamination of the recorded movies.

Histopathological diagnosis

Formalin-fixed, paraffin-embedded tumor tissue as well as normal parenchyma obtained from the contralateral thyroid lobe of each case were stained by hematoxylin and eosin. The histological diagnosis was made blindly by two independent pathologists, according to the World Health Organization guidelines (28). When the results were discordant, agreement was found by conjoint reexamination of each case.

Statistical analysis

Parametric tests were used for statistical evaluation. Results obtained in different groups of subjects were compared using the χ^2 test, Student's *t* test for paired data and logistic regression analysis. Predictivity was assessed using the Galen and Gambino test (29).

Results

Histology

Of 92 cases, 31 (34%) had a final diagnosis of malignancy on histology: 28 papillary thyroid carcinomas, including 18 classic variant, seven follicular variant, and three tall cell variant; two minimally invasive follicular carcinomas; and one medullary carcinoma. Of 92 nodules, 61 (66%) were benign at histology: 48 follicular adenomas, 11 hyperplastic nodules, and two oxyphilic adenomas.

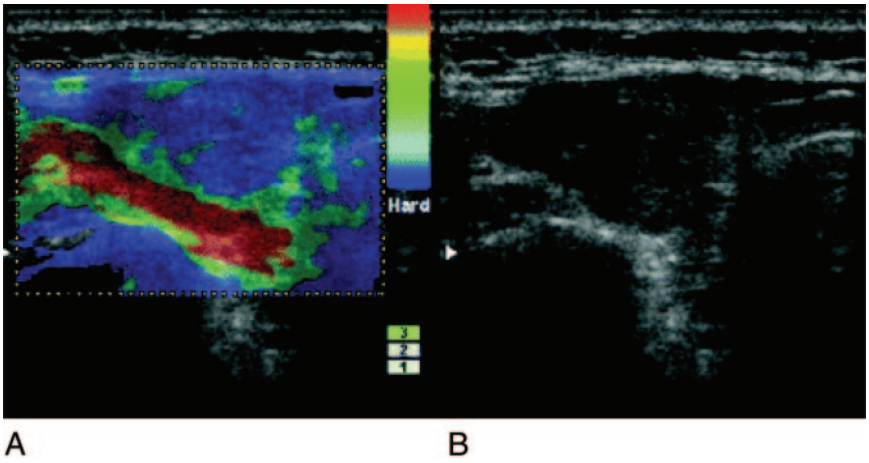

FIG. 2. Thyroid nodule images obtained on US elastography with elasticity score 5 (A) and conventional US (B).

TABLE 1. Elasticity score (32)

Score	
1	Elasticity in the whole nodule
2	Elasticity in a large part of the nodule
3	Elasticity only at the peripheral part of the nodule
4	No elasticity in the nodule
5	No elasticity in the nodule and in the posterior shadowing

Conventional US

Nodule hypoechogenicity (sensitivity 81% and specificity 62%; $P < 0.0001$), absent halo sign (sensitivity 61% and specificity 82%; $P < 0.0001$), spot microcalcifications (sensitivity 64% and specificity 72%; $P < 0.0007$) were the US patterns most predictive of malignancy. The pattern of intranodular blood flow, taken alone, was not predictive of malignancy (sensitivity 6.4% and specificity 97%; $P = 0.4$) (Table 2). As previously shown (14), the combination of echographic patterns increased the specificity but decreased the sensitivity of thyroid US. The absence of halo sign combined with the presence of spot microcalcifications was the most predictive of malignancy (sensitivity 61% and specificity 95%; $P < 0.0001$) (Table 3).

US Elastography

On US elastography: score 1 was found in 41 cases, all benign lesions; score 2 in eight cases, all benign; score 3 in 13 cases, one carcinoma and 12 benign; score 4 in 16 cases, all carcinomas; and score 5 in 14 cases, all carcinomas. Thus, all 61 cases with a final diagnosis of benign nodule had a score of 1–3, while 30 of 31 (96.7%) with a final diagnosis of carcinoma had a score of 4–5 ($P < 0.0001$), with a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 98%. One of 31 nodules (3.3%) with the histological diagnosis of papillary cancer had a score of 3. Among benign lesions, the score was 1 in seven and 2 in four of the 11 hyperplastic nodules; it was 1 in 34, 2 in four, and 3 in 12 of the 50 adenomatous nodules. Although the number of hyperplastic nodules is too small to allow a reliable statistical evaluation, these data suggest that adenomatous nodules have a higher stiffness with respect to the hyperplastic nodules. The predictivity of US elastographic measurement was independent from the nodule size, high sensitivity and specificity being observed also in nine nodules that had the highest diameter comprised between 0.8 and 1 cm, submitted to surgery for a FNA result suggestive or suspicious of papillary thyroid cancer (five cases) or indeterminate lesion (four cases). Five of these nine nodules had a score of 4–5, and in all of them, the histological diagnosis of carcinoma was confirmed. In four nodules the elasticity score was 1–3, and the histological diagnosis was follicular adenoma in three cases and hyperplastic nodule in one case (Table 4). Thus, the possibility to select the area of US elastography analysis allowed a correct scoring, even of these small nodules, independently from their position within the thyroid lobe. When the data were analyzed by logistic regression, the elastographic score was an independent predictor of the final histological diagnosis as the score 4–5 was in all cases but one coincident with the diagnosis of cancer. Both the absent halo sign ($r = -0.2$; $P = 0.005$; $X_2 = 7.8$) and the presence of spot microcalcifications ($r = 0.19$; $P = 0.01$; $X_2 = 6.4$) were independently associated with the elastographic score 4–5. As expected, the same results were obtained when the final histological diagnosis was taken as the dependent variable.

Of the 32 patients with a FNA result of indeterminate (follicular) lesion, 25 had a benign follicular adenoma on histology and seven a carcinoma: one papillary, classic variant; four papillary follicular variants; and two minimally invasive follicular carcinomas. The conventional US, as previously shown in a larger series of patients (37), was not predictive in these patients. At variance, an US elastography score of 4–5 was observed in six of seven (86%) patients with carcinoma and a score of 1–3 in all 25 patients with benign lesions (Table 5).

In the four patients with nodules showing a calcified shell, the US elastogram was not valuable because the US beam does not cross the calcifications, and no tissue strain was obtained by the probe pressure. Similarly, US elastogram results were considered unreliable in the four patients with completely cystic nodules because nodule elasticity was dependent on the liquid content and not on the solid wall (data not shown). Thus, nodules showing these US characters are not suitable for evaluation by US elastography. Of the 92 cases included in the study, four were solid nodules with anechoic lacunae that occupied less than 20% of the nodule volume. These four nodules had an US elastography score of 1, with a final diagnosis of follicular adenoma on histology.

TABLE 2. Predictivity of thyroid US patterns in patients with thyroid nodules that resulted in benign lesions (BN) or carcinoma (CA) on histology

	BN (n = 61)	CA (n = 31)	*P* value	Sensitivity (%)	Specificity (%)
Hypoechogenicity			0.0001	81	62
Present	23	25			
Absent	38	6			
Halo sign			<0.0001	61	82
Present	50	12			
Absent	11	19			
Spot microcalcifications			<0.0007	64	72
Present	17	20			
Absent	44	11			
Type III vascularization			0.48	6.4	97
Present	2	2			
Absent	59	29			

TABLE 3. Predictivity of combinations of thyroid US patterns in patients with thyroid nodules that resulted in benign lesions (BN) or carcinoma (CA) on histology

	BN (n = 61)	CA (n = 31)	*P* value	Sensitivity (%)	Specificity (%)
Absent halo sign/hypoechogenicity			<0.0001	58	93
Both present	4	18			
One absent	57	13			
Absent halo sign/spot microcalcifications			<0.0001	61	95
Both present	3	19			
One absent	58	12			
Hypoechogenicity/spot microcalcifications			<0.0001	52	90
Both present	6	16			
One absent	55	15			
Absent halo sign/hypoechogenicity/type III vascularization			0.1	3.2	100
All present	0	1			
One absent	61	30			
Hypoechogenicity/spot microcalcifications/type III vascularization			0.1	6.4	100
All present	0	2			
One absent	61	29			
Absent halo sign/spot microcalcifications/type III vascularization			0.1	3.2	100
All present	0	1			
One absent	61	30			

Discussion

The elasticity of tissues has been studied by several authors with different approaches (30). US elastography is a newly developed dynamic technique that evaluates the degree of distortion of a tissue under the application of an external force, and is based upon the principle that the softer parts of tissues deform easier than the harder parts under compression, thus allowing an objective determination of tissue consistency (21, 22). Malignant lesions are often associated with changes in the mechanical properties of a tissue, and US elastography has been used to differentiate cancers from benign lesions in prostate, breast, pancreas, and lymph nodes (23, 24, 31–35). As far as the thyroid is concerned, there is only one report using US elastography (25). In this paper the authors studied 31 patients with nodular goiter, using both a real-time elastography on adapted US scanner and an off-line processing of strain images reconstructed from radiofrequencies data stored during US examination. Only with the off-line processing was it possible to compare the stiffness of benign and malignant lesions for the differential diagnosis of thyroid cancer, with a specificity of 96% and a sensitivity of 82% being reported. However, this method is labor intensive and time consuming (25). In our study we have used on a larger group of patients a newly developed US apparatus by which the freehand compression applied on the neck region was standardized by real-time measurement on a numerical scale, rendering highly reproducible the real-time determination of tissue elasticity. This technical implementation minimizes the artifacts reported by Lyshchik *et al.* (25), and reduces the interobserver and intraobserver variability. This technique is easy to perform and requires no more than 3–5 min of additional examination time to conventional US, so it can be proposed during routine US thyroid evaluation.

In our study group, the highest elasticity scores, indicative of a greater nodular consistency, were invariably associated with malignancy with minimal loss of sensitivity (specificity 100%, sensitivity 97%). The predictivity of US elastographic measurement was independent from the nodule size, high sensitivity and specificity being observed also in nine nodules that had the highest diameter comprised between 0.8 and 1 cm, submitted to surgery for a FNA result suggestive or suspicious of papillary thyroid cancer (five cases) or indeterminate lesion (four cases). The possibility to select the area of US elastography analysis allowed a correct scoring, even of these small nodules, independently from the position of the nodule within the thyroid lobe. These results go beyond our more optimistic expectations and, if confirmed, would render US elastography the best available noninvasive tool for the evaluation of thyroid nodules, comparable to FNA. However, it is important to note that our study group included a select population in which thyroid surgery

TABLE 4. Predictive value of US elastography in patients with thyroid nodules that resulted in benign lesions (BN) or carcinoma (CA) on histology

Size	Score	BN (n = 61)	CA (n = 31)	*P* value	Sensitivity (%)	Specificity (%)
0.8–1 cm	1–3	4	0	0.002	100	100
	4–5	0	5			
1.1–2 cm	1–3	12	0	<0.0001	100	100
	4–5	0	16			
>2 cm	1–3	42	1	<0.0001	90	100
	4–5	0	9			
All	1–3	61	1	<0.0001	97	100
	4–5	0	30			

TABLE 5. Predictive value of US and US elastography in 32 patients with indeterminate thyroid nodule on FNA

	BN (n = 25)	CA (n = 7)	*P* value
Hypoechogenicity on US			0.1
Present	14	6	
Absent	11	1	
Halo sign on US			0.6
Present	24	7	
Absent	1	0	
Spot microcalcifications on US			0.8
Present	6	2	
Absent	19	5	
Type III vascularization on US			0.5
Present	1	0	
Absent	24	7	
Score 1–3 on US elastography	25	1	<0.0001
Score 4–5 on US elastography	0	6	

BN, Benign lesions; CA, carcinoma.

had been already planned because of cytological suspicion or large nodular size. This could represent a bias that amplifies the predictive value of US elastography.

Although presently, FNA remains the most important procedure for the diagnostic management of thyroid nodules, yet a substantial proportion (up to 20%) of cytological specimens yield indeterminate results (36), and the distinction between benign and malignant lesions can only be made on histological criteria. In follicular lesions, conventional echographic patterns were found to be of minor relevance (37) for predicting carcinoma. These results have been confirmed in the present series of 32 patients with indeterminate nodules on cytology, seven of whom resulted to have a papillary or follicular thyroid carcinoma on histology. The predictivity of US elastography in this subgroup of patients was highly rewarding, scores 4–5 being found in six of seven patients having a final diagnosis of malignancy and a score of 1–3 in all 25 patients with a histological diagnosis of benign lesion.

On the other hand, conventional US maintains a pivotal importance to define which nodules are suitable for the US elastographic characterization. Indeed, nodules in which US reveals the presence of calcified shell have to be excluded from the US elastographic evaluation because the US beam does not cross the calcification, and the probe compression does not result in tissue strain deformation. Similarly, in cystic nodules, US elastography cannot give useful information, the main determinant of nodule stiffness being the fluid content, and not the solid wall. For this reason, we selected 92 patients who had solid nodules for the analysis. Only in four cases were anechoic lacunae present within the nodule that occupied less than 20% of the nodule volume. Further studies will be necessary to understand whether US elastographic measurements can give reliable results in nodules that are greater than 20% cystic. One other limitation of this technique is that the nodule to be examined must be clearly distinguishable from other nodules present in the thyroid, to select it for the US elastography measurement. Thus, multinodular goiters with coalescent nodules in most cases are not suitable for this analysis.

In conclusion, US elastography seems to have great potential as a new tool for the diagnosis of thyroid cancer, especially in nodules with indeterminate cytology. Larger prospective studies are needed to confirm our results and establish the diagnostic accuracy of this technique.

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Address all correspondence and requests for reprints to: Paolo Vitti, M.D., Department of Endocrinology, University of Pisa, Via Paradisa, 2, 56124 Pisa, Italy. E-mail: p.vitti@endoc.med.unipi.it.

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